REMARKS

Reconsideration of the present application, as amended, is respectfully requested.

A. STATUS OF THE CLAIMS

As result of the present amendment, claims 12-13 and 16-21 remain in the case for continued prosecution.

Claims 12 and 16 have been amended to remove informalities.

Claim 17 has been amended to remove compound 19.

No new matter has been added.

B. CLAIM REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

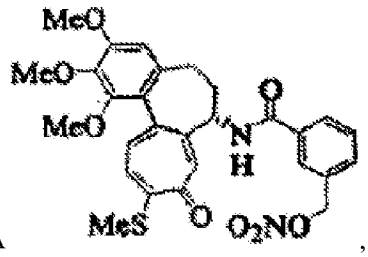
On page 3, claims 17 and 20-21 are rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. The Examiner indicated that claim 17 recites compounds 19 and 29-32 and there is insufficient antecedent basis for these compounds.

Applicants respectfully traverse. Applicants respectfully would like to draw the Examiner's attention that claims 17 does not depend from claim 12 or Formula 1. Thus, it is respectfully urged that the rejection is not proper and obviated. Nevertheless, compound 19 has been removed from claim 17.

For all of the reasons above, reconsideration and withdrawal of this rejection is respectfully requested.

C. CLAIM REJECTIONS UNDER 35 U.S.C. § 103(a)

On page 3-9, claims 12-13 and 16-21 are rejected under 35 U.S.C. § 103(a), for allegedly being unpatentable over Kim et al. (WO 02/100824) in view of Patani et al. (Chem. Rev. (1996) 96:3147-3176). The Examiner indicated that Kim et al. teach Compound A and compounds in the instant claims are merely different by having fluorine on the phenyl ring.

Compound A 

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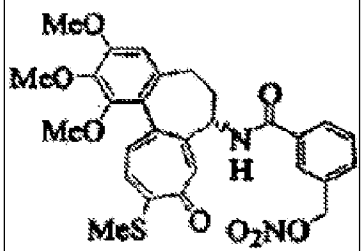
Applicants respectfully traverse. Applicants respectfully would like to draw the Examiner's attention substitution of hydrogen with fluorine is not an obvious isosteric replacements. In addition, the following explanation provides evidence that it is unpredictable how the introduction of fluorine would change the biological activities of the compound and thus, it is not an obvious choice for chemist to substitute hydrogen with fluorine.

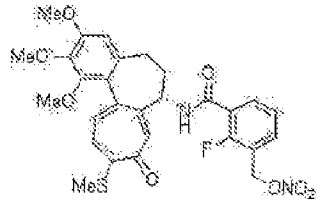
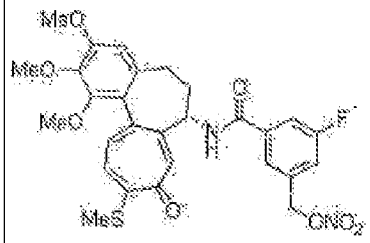
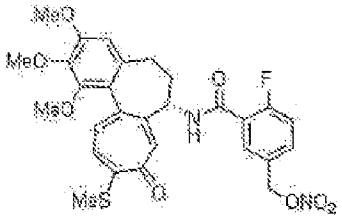
-Fluorinated compound with superior anticancer activity-

First of all, the present invention provides the anticancer activities of the inventive compounds including compounds 10, 12, and 17, which are fluorinated on various positions on Compound A. KIM and the present invention both measured their anti-cancer efficacy of the compound against several cancer cell lines using a known anti-cancer agent, paclitaxel, as the control. Table 1 and 2 provides analysis of their activities against paclitaxel. It is noted that there are three common cancer cell lines these compounds were tested against, A549, SK-OV-3 and MCF-7. The compounds of the present invention shows equal or significant improvement in several cell lines compared to Compound A. The data marked as "*" shows that the compounds in the present invention can be 2-15 times more effective than Compound A. Especially for MCF-7 cell line, Compounds 10, 12 and 17 of the instant invention shows predominantly superior efficacy than Compound A.

[Table 1] Cytotoxicity to cancer cell lines for compound 12 (Compound A) of Kim et al., data from Table

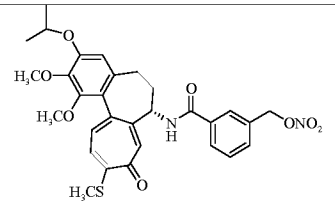
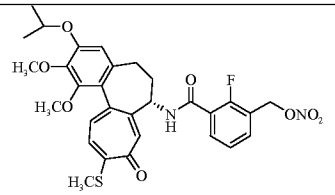
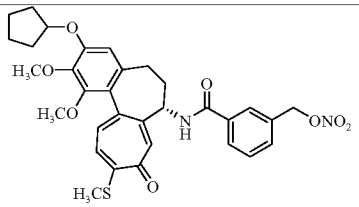
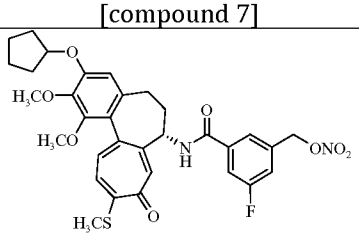
	Cytotoxicity [ED_{50}: nM]				
Cell line	A549	SK-OV-3	SK-MEL-2	HCT15	MCF-7
Taxol	0.3	1.2	0.1	0.1	0.04
Example 12	0.1	0.3	0.1	0.1	0.2
(Compound A) 	3 times	4 times	1 times	1 times	0.2 times

[Table 2] Cytotoxicity to cancer cell lines for compounds 10, 12 and 17 of present invention, data from Table 1 on pages 139-140 of the present application.

	Cytotoxicity [ED_{50}: nM]				
Cell line	**A549**	**SK-OV-3**	**SK-MEL-2**	**HCT15**	**MCF-7**
Paclitaxel	**0.3**	**1.2**	**0.1**	**0.1**	**0.9**
Cpd. 10 	0.28	0.23	0.12	0.39	0.09
	1 times	4 times	1 times	0.25 times	10 TIMES*
Cpd. 12 	0.05	0.27	0.11	0.05	0.03
	6 TIMES*	4 times	1 times	2 TIMES*A	30 TIMES*
Cpd. 17 	0.21	0.19	0.17	0.19	0.08
	1.5 times	6 TIMES*	1 times	0.5 times	11 TIMES*

A similar effect of fluoride on the biological activity can be also found among the compounds in the present application. Compounds 9 and 15 are fluorinated counterpart of compounds 3 and 7, respectively.

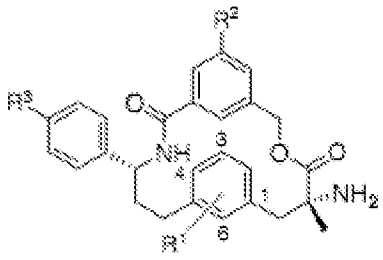
[Table 3] Compounds in the present application with H vs. F

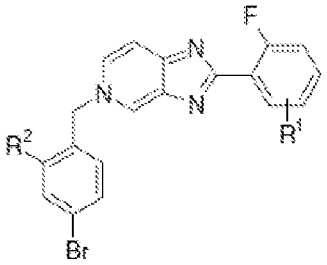
	Cytotoxicity [ED_{50}: nM]				
Cell lines	**A549**	**SK-OV-3**	**SK-MEL-2**	**HCT15**	**MCF-7**
 [compound 3]	2.4	4.0	1.0	4.8	2.3
 [compound 9]	0.49	0.34	0.22	0.64	0.13
 [compound 7]	>50	>50	>50	>50	>50
 [compound 15]	30.2	>50	22.5	23.4	18.8

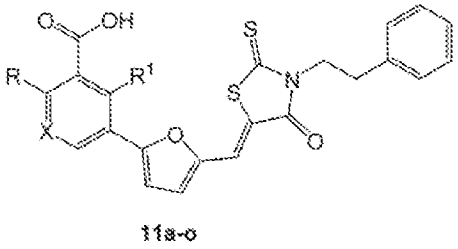
-Fluorinated compounds with reduced biological activity-

On the other hand, substitution of fluorinated is not always obviously expected to improve the biological activity of the compounds. Some experimental report known to those skilled in the art can also teach away or discourage those ordinary skilled in the art from making fluorinated compounds randomly. Applicant respectfully provides the following data from non-patent literature wherein fluorination reduced the biological activity of a compound. In the following publications, many fluorinated compounds have reduced biological activities compared to their non-fluorinated counterpart.

[Table 4] Compounds in the literature wherein F reduces activity

<table>
<tr><th>Compound</th><th>Result</th></tr>
<tr><td>Exhibit_BMCL_4057
  </td><td>This publication reports Structure-Activity Relation (SAR) of BACE-1 inhibitors. The result in Table 2 shows that the fluorinated Compound 6c (R^1=F, R^2=2-CN-Ph, R^3=F) has a much lower activity than non-fluorinated compound 6b (R^1=H, R^2=2-CN-Ph, R^3=H) (IC_{50} 6b=27nM, 6c=130nM). Similarly, fluorinated Compound 6g (R^1=F) has lwer activity than the non-fluorinated Compound 6f (R^1=H) (IC_{50} 6f=22nM, 6g=46nM).

<table>
<tr><th>Compound</th><th>R^1</th><th>R^2</th><th>BACE-1 IC_{50} (nM)</th></tr>
<tr><td>6b</td><td>H</td><td>2-CN-Ph</td><td>27</td></tr>
<tr><td>6c</td><td>3-F</td><td>2-CN-Ph</td><td>130</td></tr>
<tr><td>6f</td><td>H</td><td>2-CN-3-F-Ph</td><td>22</td></tr>
<tr><td>6g</td><td>4-F</td><td>2-CN-3-F-Ph</td><td>46</td></tr>
</table>
</td></tr>
<tr><td>Exhibit_BMCL_5111
  </td><td>This publication relates to comparative study for anti-BVDV 및 anti-HCV activity. Table 1 provides anti-BVDV, and anti-HCV activities, wherein Compound 1 has better activity than the fluorinated derivatives, Compounds 2, 3, 5, and 6 in its anti-BVDV activity. In addition, while their anti-HCV activity has mixed result.

<table>
<tr><th>Compound</th><th>R^1</th><th>R^2</th><th>BVDV EC_{50} (mM)</th><th>HCV EC_{50} (mM)</th></tr>
<tr><td>1</td><td>H</td><td>H</td><td>0.12</td><td>3.0</td></tr>
<tr><td>2</td><td>3-F</td><td>H</td><td>0.24</td><td>0.6</td></tr>
<tr><td>3</td><td>5-F</td><td>H</td><td>0.50</td><td>45</td></tr>
<tr><td>5</td><td>6-F</td><td>H</td><td>0.48</td><td>75</td></tr>
</table>
</td></tr>
<tr><td>Exhibit_JMC_7631
 
11a-o</td><td>This reference relates to SAR of HIV-1 inhibitor. Table 3 presents anti-HIV=1 activity and selectivity Indexes, wherein the fluorinated compound 11e (R=F) has lower activity than the non-fluorinated Compound 11a (R=H).

<table>
<tr><th>Compound</th><th>X</th><th>R</th></tr>
<tr><td>11a</td><td>CH</td><td>H</td></tr>
<tr><td>11e</td><td>CH</td><td>F</td></tr>
</table>
</td></tr>
</table>

These results, in addition to the data in the present application support that the substitution of H with F is not an obvious variation of the compounds from the prior art. On page 7-8 of Office Action, the Examiner provides several examples with contradicting conclusions: On page 7, it was indicated that Patani teaches the substitution of H with F should not alter the

biological/pharmaceutical properties but, on page 8 it was indicated that there would be a reasonable expectation of success in this modification.

The physico-chemical properties may not change much by substitution of H with F. However, the substitution cannot be made a simple one-step substitution reaction in most of the compounds. In the present invention, most fluorinated compounds were not prepared from their non-fluorinated counterpart by fluorine substitution but prepared from a different starting material from several steps in advance. In other words, the compounds having F requires a different synthesis process and thus it would not have been an easy and obvious choice to those ordinary skilled in the art but would require much endeavor enough to make the choice NON-OBVIOUS.

It was noted that the Examiner indicated that, based on the prior teaching and the other examples in the court, substitution of H with F would not result in any dramatic changes but a equal or some improvement, and thus obvious variation. Applicant respectfully disagrees and would like to reemphasize the result presented in Tables 1 and 2 of this response, wherein the fluorinated compounds made SIGNIFICANT IMPROVEMENT in their biological activity, in contrary to what was known in the art, over the non-fluorinated compound A.

On page 9, claims 18-21 are rejected based on the anti-cancer activity of Compound A of teachings by Kim. Applicant respectfully disagrees. As provided in the above Tables 1-2, the compounds in the instant claims were not merely as effective as the compounds by Kim but provided SIGNIFICANTLY BETTER ACTIVITY. However, considering other references such as three Exhibits enclosed, other publications teach away from the reasonable expectation of success and thus, it is respectfully urged that the present invention and the instant claims are NOT OBVIOUS over the teachings by the cited references separately or in combination.

In summary, considering the difficulties of preparing fluorinated derivatives, the unexpected but significantly improved biological activities, and teaching away references available to those ordinary skilled in the art, the present invention and the instant claims are NOT OBVIOUS over the teachings by the cited references separately or in combination.

For all of the amendments and reasons above, reconsideration and withdrawal of this and future rejections is respectfully requested.

D. CLAIM REJECTIONS DUE TO DOUBLE PATENTING

On pages 9-11, all pending claims are rejected on the ground of non-statutory obviousness-type double patenting over claims of US 7,119,229 in view of Patani et al. or over claims of US 7,622,612. Applicants respectfully traverse and requests to hold the rejection abeyance until allowable subject matter is determined.

E. FEES

This response is being filed timely with a petition for three (3) month extension of time and the required fee. Thus, no further fee is believed to be required. If, on the other hand, it is determined that any fees are due or any overpayment has been made, the Assistant Commissioner is hereby authorized to debit or credit such sum to Deposit Account No. 02-2275.

Pursuant to 37 C.F.R. 1.136(a)(3), please treat this and any concurrent or future reply in this application that requires a petition for an extension of time for its timely submission as incorporating a petition for extension of time for the appropriate length of time. The fee associated therewith is to be charged to Deposit Account No. 02-2275.

An early and favorable action on the merits is earnestly solicited.

F. CONCLUSION

In view of the actions taken and arguments presented, it is respectfully submitted that each and every one of the matters raised by the Examiner have been addressed by the present amendment and that the present application is now in condition for allowance. However, Applicants reserve the right to respond to any outstanding issues which have not been addressed in this response. Furthermore, it is respectfully urged that the Examiner contact the undersigned with any question.

An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,

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